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Langerhans Cell Histiocytosis in the Adult

J. S. Malpas and A. J. Norton

A study of 47 well-documented patients with Langerhans cell histiocytosis (LCH) showed a slight female preponderance, with onset as late as the ninth decade. The skin was the commonest site of presentation, but pulmonary and bone involvement was frequent. Patients with single-site disease did best. The worst prognosis was seen in the elderly or those with organ dysfunction. A high incidence of associated malignant disease was seen, which could precede, be coincidental with, or occur after a diagnosis of LCH. © 1996 Wiley-Liss, Inc.

Key words: Langerhans cell histiocytosis, adult, clinical features, treatment, malignant disease

INTRODUCTION

Langerhans cell histiocytosis (LCH) is a rare condition in adults. With the recent recognition of the clonality of the disorder [1], interest in its manifestations in the adult patient and its association with malignancy has been renewed. The need for epidemiological studies is evident [2] and a review of its clinical course in the adult and its significance as a rare but important differential diagnosis of multiple myeloma, lymphoma and various endocrinopathies is evident. In order to review the clinical course of LCH, 16 patients treated at St. Bartholomew's Hospital, London over 25 years, together with a further 31 patients identified in the world literature, for whom adequate information was available, were studied.

PATIENT POPULATION

A total of 47 patients over age 15 years were included. The retrospective review of the literature includes patients in whom the histology was available and where the clinical presentation, response to therapy and eventual outcome were recorded. In the institutional series, patients referred for a second opinion in whom follow-up was inadequate, were excluded. Published series of patients with a single-site presentation, such as bone, central nervous system or thyroid, were not included as they might have biased the findings.

METHODS

The clinical and pathological data from 47 adult patients are presented by stage, those with single-site disease in Table I, with multi-site disease in Table II and multi-site disease with organ failure in Table III. Organ dysfunction or failure was defined as the presence of impaired pulmonary function tests in association with classical chest radiography, abnormal liver function tests and persistent anaemia, leukopenia with or without thrombocytopenia as a result of bone marrow failure due to LCH. It did not include patients with diabetes insipidus as a result of posterior pituitary damage.

All patients had histology available for assessment, although in three this only became available at autopsy. The three terms that reflect confidence levels of diagnosis, recommended by the Writing Group of the Histiocyte Society [3], namely "definitive diagnosis," "diagnosis" and "presumptive diagnosis," have been used. The Writing Group considered that lesional cells with Birbeck-Breatnach granules or CD1a (OKT6) or both are required for a definitive diagnosis. The presence of Birbeck-Breatnach granules is now considered pathognomonic for the LCH cell, and distinguishes the cell from the normal Langerhans cell [4]. The use of monoclonal antibody CD1a (O10) on routinely paraffin-embedded samples, and its value in the definition of LCH has been described recently [5]. The presence of histiocytic infiltration with classical features of the disease, such as diabetes insipidus, was considered to establish the diagnosis, while in patients with fibrous tissue and/or foam cells present in biopsies with no residual histiocytes but who otherwise had undoubted features of LCH, a "presumptive" diagnosis could be made. Only patients with a substantial follow-up were included and when death was recorded the manner of death was noted. Other major acute or chronic illnesses were recorded and particular note taken of any associated malignant disease and its relation to the occurrence of LCH.

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TABLE I. Langerhans Cell Histiocytosis in the Adult: Single Site*

Case no.	Gender	Age	Presentation and progress	Histology	Follow-up	Treatment	Malignancy	Relation to LCH	Ref. no.
1	M	75	S→L DI DM	Def	Alive	None	No		12
2	M	62	S	Def	Alive 20 yr+	RT to skin	No		13
3	M	76	S	Def	Died 15 days with heart failure	None	No		15
4	F	60	S	Def	Died 6 yr+	None	No		17
5	F	54	S→L	Def	Died 3 mths not LCH	PUVA	No		21
6	M	41	S	Def	Alive 9 yr+	Electron beam RT to skin	No		25
7	F	44	S	Def	Died 3 mths+ due to myeloma	VMCP for myeloma[a]	Myeloma	Myeloma preceded LCH	27
8	F	19	B	Def	Alive	No	No		30
9	M	15	B	Pres	Alive	No	No		30
10	F	26	B	Def	Alive	RT and Chemotherapy	No		30
11	F	37	B	Diag	Alive	No	No		30
12	M	43	DI	Def	Alive	RT → Etoposide	Philadelphia+ CML	CML 4 yrs after LCH	30
13	M	21	B	Pres	Alive	No	No		30
14	F	38	B	Pres	Alive	No	No		30
15	M	19	B	Diag	Alive	No	Ewings Sarcoma	LCH 13 yrs after Ewings sarcoma	30
16	F	37	B	Diag	Alive	No	Breast cancer	Concurrent	3
Present			Presumptive diagnosis	Diag	Diagnostic	Def	Definitive Diagnosis		

*Abbreviations for Tables I–III. P, pulmonary symptoms and signs; S, skin; Wt loss, weight loss; VMCP, vinblastine, melphalan, cyclophosphamide and prednisolone; Pres, presumptive diagnosis; DI, diabetes insipidus; DM, diabetes mellitus; N, neurological signs and symptoms; Diag, diagnostic; L, lymphadenopathy-splenomegaly; B, bone involvement, VLB, vinblastine; RT, radiotherapy; Def, definitive diagnosis.

Treatments were documented in nearly all patients and whenever possible, response was noted.

RESULTS

Clinical Manifestations

Patient ages ranged from 15 to 91 years with slightly more females than males (Table IV). Skin rashes, mostly described as resembling seborrheic dermatitis, were the most frequent primary manifestation. Involvement could be extensive and debilitating. Breathlessness and polydipsia and polyuria were also frequent (Table V). The high incidence of diabetes insipidus might be attributed to the well-known endocrine interests of the single institution, but the high incidence of breathlessness with associated lung dysfunction in the adults is notable (Table III). Fever, with sometimes drenching sweats and loss of weight, were the next most common symptoms and often raised the suspicion of the presence of lymphoma. Pain was a frequent symptom and was usually the result of lytic lesions in the weight-bearing part of the skeleton. Painful skull lesions were, however, noted and the presence of pain could sometimes distinguish these lytic lesions from myeloma where they are usually painless. Although lymphadenopathy and splenomegaly are said to be uncommon in adults, 11 patients (23%) showed this feature in the present series.

The commonest sites of presentation were skin, lung and bone (Table VI) although the occurrence of diabetes insipidus and involvement of the lymphoreticular system was high in the adult series. In those presenting with a single site, few patients were ill enough to require systemic therapy and only one died of LCH (6%; Table VII). These patients either showed spontaneous healing or progressed along a relapsing and remitting course. Patients who presented with multiple site disease (Table II) most commonly had fever and weight loss, and this group had a relatively high incidence of serious skin problems. Progressive disease eventually resulting in death was more common and 5 (25%) died with LCH. In patients with multiple site disease and organ dysfunction, the commonest organ affected was the lungs. Acute pulmonary symptoms from spontaneous pneumothoraces were sometimes a presenting feature and occurred in 2 cases, case 7 and case 15. Usually, however, slow progressive lung dysfunction was seen. Eight out of 11 patients in this group (Table III) had significant lung involvement and in the stage as a whole 4 /11 (36%) died of LCH. Other intercurrent diseases such as bronchopneumonia

TABLE II. Langerhans Cell Histiocytosis in the Adult: Multiple Site

Case no.	Gender	Age	Presentation and progress	Histology	Follow-up	Treatment	Malignancy	Relation to LCH	Ref. no.
17	F	67	SLB wt loss	Diag	Died after 3 mths	None	Urinary light chain/MM	Concurrent myeloma and LCH	7
18	M	70	S→P wt loss	Diag	Alive	VLB and steroids	No		8
19	M	52	S→DI DM	Diag	Alive	Local steroids	No		11
20	F	54	DI B	Diag	Alive 13 yr+	None	No		14
21	M	74	P L	Def	Died at 3 mths	Busulphan	No		18
22	F	65	S wt loss P	Diag[a]	Died at 2 yrs	Local steroids	No		18
23	F	91	S→B	Def	Died at 3 mths	Systemic and topical steroids	Lymphocytic lymphoma	LCH preceded lymphoma	18
24	F	60	S→wt loss P	Diag	Died at 8 yr+	Vitamin A response	No		18
25	F	81	S→P	Diag	Died at 2 wks Broncho-pneumonia	Steroids[b] Thyroxin	No		18
26	F	81	S→wt loss L	Def	Died at 9 mths Broncho-pneumonia	Steroids and VLB	No		19
27	M	20	S→P L	Def	Died after 2 yrs with LCH	Chemotherapy	No		22
28	F	67	S→wt loss acute pan-creatitis	Def	Died 1st admission	None	No		23
29	F	16	DI thyroiditis wt loss L	Def	Alive	Steroids then cyclophos-phamide	No		24
30	M	45	N and DI → S	Def	Died after 4 yrs	Interferon	No		26
31	M	72	Di wt loss B and P	Diag+	Alive	None	No		28
32	M	37	B and DI	Def	Alive	RT Chemotherapy	No		30
33	F	35	DI and S	Diag	Alive	RT steroids	Hypothalamic tumour	LCH preceded tumour	30
34	M	40	B and DI	Def	Alive	RT	No		30
35	F	54	B and wt loss	Diag	Alive	None	Breast cancer	LCH followed cancer by 10 yrs	30
36	F	23	DI and L	Diag	Alive	VLB and steroids	No		30

[b] Present: Hypothyroid Presumptive diagnosis

Histology: Diag + Diagnostic; Def Definitive Diagnosis

Follow-up: Possible Erdheim Chester Disease

[a] Post mortem confirmation

or heart failure caused a high mortality in this stage (Table VII).

Histology

The diagnosis was confirmed wherever possible by biopsy (Table VIII). More than half the patients had their diagnosis confirmed and only three were placed in the "presumptive" category, the "definitive diagnosis" and diagnostic groups forming 44 /47 (93%) of the patients studied. Some patients in the retrospective series were diagnosed before CD1a antibody, effective in wax-embedded tissues as clone O10 [5], was available, and in the institutional series biopsy material sometimes proved unsuitable technically for immunohistochemical staining.

TREATMENT

While local therapy with either curettage of bone lesions or radiotherapy was quite frequently used, multisystem disease or the presence of life-threatening organ dysfunction was an indication for systemic therapy. Chemotherapy either with single agents or single agents together with steroids was the treatment most commonly used (Table IX). Fourteen patients were treated in this way. Vinblastine was most frequently used by cyclophosphamide and etoposide were also prescribed, the latter proving successful on the two occasions when it was given. A total of 5 complete, 2 good partial and 3 partial responses were recorded, giving an overall response rate

TABLE III. Langerhans Cell Histiocytosis in the Adult: Multisite and Organ Dysfunction

Case no.	Gender	Age	Presentation and progress	Histology	Follow-up	Treatment	Malignancy	Relation to LCH	Ref. no.
37	M	30	DI P poor respiratory function	Diag	Died after 3 yrs	None	No		6
38	M	32	P→wt loss S pulmonary dysfunction	Diag	Alive at 8 yrs	Steroids	No		9
39	F	16	P S L→BM failure	Diag[a]	Died after a few days	High dose steroids	No		10
40	F	37	S→P→DI DM L poor respiratory function, liver dysfunction	Def	Died with liver failure	VLB steroids	No		17
41	F	65	S→poor respiratory function	Diag	Died at 6 wks cardiac failure	VLB	No		17
42	M	69	S→P poor respiratory function	Def[a]	Died of Broncho-pneumonia	None	No		18
43	M	62	P→S poor respiratory function	Def	Died 6 mths of LCH	None	No		18
44	F	69	S P BM failure	Def	Died after 4 mths of LCH	None	No		18
45	F	61	S L B Liver dysfunction	Def	Alive	None	No		29
46	M	49	DI L P poor respiratory function	Def	Alive	VLB and steroids	No		30
47	F	26	B→P poor respiratory function	Diag	Alive	Steroids	No		30

[a]Histology from postmortem.

TABLE IV. Patient Characteristics

Number of patients with LCH	47
Gender	
Male	21
Female	26
Age	
Mean	49 yrs
Median	62 yrs
Range	15 to 91 yrs

TABLE V. Patient Symptomatology

Presenting symptoms	Number
Skin rash	26
Dyspnoea	13
Thirst and polyuria	13
Pain	12
Lymphadenopathy and/or splenomegaly	9
Loss of weight	8
Fever	7
Gum hypertrophy, arthralgia, aural discharge, ataxia and amnesia also recorded	

TABLE VI. Sites of Disease at Presentation and Subsequently

Site	Number of patients (%)
Skin	27
Lung	16
Bone	16
Posterior pituitary	11
Lymphatic system	11
Thyroid	2
Central nervous system	1

of 70%. Local injection of methyl prednisolone was effective but disappointing results were achieved with cyclosporin and interferon in this series.

ASSOCIATED DISEASE

A feature of this series was the high incidence of malignancy (Table X). A total of 8 patients (17%) had an associated haematological or solid tumour. In one patient, LCH was treated with etoposide and 4 years later a diagnosis of Philadelphia-positive chronic myeloid leukaemia was made. In 3 patients the malignancy preceded the development of LCH; in 2 it was concurrent and in a

TABLE VII. Causes of Death in Adults With LCH

	Number	Total deaths (%)	Due to LCH (%)	Due to other disease[a] (%)	Malignancy (%)
Single site	16	4 (25)	1 (6)	2 (12)	1 (6)
Multiple site	20	10 (50)	5 (25)	3 (15)	2 (10)
Multiple site	11	7 (63)	4 (36)	3 (27)	0

[a]Includes bronchopneumonia and congestive cardiac failure.

TABLE VIII. Reliability of Histological Diagnoses in 47 Patients

Characteristic histiocytic infiltration	44
"Burnt out" fibrous tissues only	3
Positive cytochemistry S100 CD1A and/or Birbeck Breatnach granules	25
Grading of LCH	
Presumptive diagnosis	3
Diagnosis	19
Definitive diagnosis	25

TABLE IX. Systemic Treatments and Response

Chemotherapy	Number	Responses
VLB + steroids	9	4CR 2GPR 2PR 1NR[a]
Cyclophosphamide + steroids	2	1CR 1PR
Etoposide + steroids	2	2CR
Busulphan	1	NR
Injection of methyl prednisolone	2	2CR
Other		
Cyclosporin	2	2NR
Interferon	1	1PR
Vitamin A	1	1PR

[a]CR, complete response; GPR, good partial response; PR, partial response; NR, no response.

TABLE X. Malignant Disease in Association With LCH

Case no.	Gender	Malignancies and relation to LCH
7	F	Bence Jones myeloma aged 39. LCH aged 46.
12	M	LCH aged 43. Treated with etoposide. Philadelphia positive chronic myeloid leukaemia aged 49.
15	M	Ewings sarcoma aged 6. Treated with radiotherapy chemotherapy. LCH aged 19.
16	F	Breast cancer and LCH aged 37.
17	F	Bence Jones myeloma and LCH aged 67.
23	F	LCH diagnosed 3 mths before lymphocytic lymphoma aged 91.
33	F	LCH aged 22. Hypothalamic tumour treated with radiotherapy aged 35.
35	F	Breast cancer aged 43. LCH/Erdheim Chester diseased aged 59.

further 3, LCH was followed by malignant disease at intervals of a few months to some 10 years.

DISCUSSION

LCH rarely affects adults, and the exact incidence is at present unknown. In large series from single institutions the number of cases of adults presenting at each institution is approximately 30% of all cases of LCH seen [31–33]. LCH can occur at any age and while it is three times more common in girls it appears that with increasing age the incidence in the sexes approaches equality. Because of its frequent involvement of the skin it forms an uncommon but important differential diagnosis of seborrheic dermatitis. In some patients purple nodular infiltrative lesions were reported which required biopsy for the diagnosis to be made. Two other important differential diagnoses in the adult are myeloma, in which lytic lesions to the skull are a feature, and lymphoma, in which lymphadenopathy, fever, sweating, splenomegaly and weight loss resembling Hodgkin's disease or non-Hodgkin lymphoma are seen. While pulmonary lesions can occur as a solitary presentation, lung involvement is more frequent as part of a systemic multisystem disease [34]. In this series, no pulmonary disease was seen in patients with single system presentations but the lung was the site most frequently involved in patients with extensive disease and organ dysfunction, and was frequently associated with death (Table III). On reviewing the presentation it appears that extent of disease correlates well with prognosis. Adult patients with single-site disease affecting bone do well, as previously reported [35]. Patients with multiple-site disease and organ dysfunction are most likely to die either directly from LCH or from other conditions such as bronchopneumonia or congestive heart failure. It is also evident that LCH occurring at the extremes of age is associated with a high mortality.

The value of chemotherapy in progressive disseminated disease is confirmed in this series. The beneficial effects of etoposide, first reported in children [36] are also seen in adults. Immune manipulation and interferon therapy were not helpful in the few adults in this series where they were used.

The association of LCH with acute leukaemia, Hodgkin's disease and various solid tumours has been noted previously [37,38]. This series underlines the frequency with which it occurs and that breast cancer is quite commonly associated. Egeler et al. [38] reported a number

of patients with LCH and cancer. A high proportion of them were associated with a particular (and rare) form of lung cancer, adenocarcinoma of the lung. These patients nearly always had malignancy concurrent with LCH. Shin et al. [37] reported a 20-year-old patient with Hodgkin's disease who developed LCH after chemotherapy. A further 21 patients in his review of the literature included 8 with Hodgkin's disease preceding LCH, including his own case, 14 with LCH and Hodgkin's disease concurrently. In a personal series of 980 patients with Hodgkin's disease treated at St. Bartholomew's Hospital, no LCH has been seen, but in another series of 659 patients with Hodgkin's disease, 2 cases of LCH were recorded [39].

The present series shows an incidence of malignancy far higher than would be expected by chance alone and it is notable that solid tumours occur and that a number of these are breast cancers, some of them occurring in relatively young patients. The fact that LCH may precede, be concurrent with or subsequent to the malignancy suggests a common aetiological factor. While a common progenitor cell might be postulated in leukaemia and lymphoma as part of a malignant histiocytic spectrum [40], it is unlikely that this could be the case where sarcomas or carcinoma are concerned. This association with malignancy will encourage the belief that eventually a nonrandom cytogenetic abnormality will be discovered in LCH and will explain its frequent occurrence in association with leukaemia, lymphoma, sarcomas and breast cancer.

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REFERENCES

1. Willman CL, McClain KL, Duncan MH, Kanapilly-Chavez L, Griffiths BB, Isaacson PE, Schnell B, Greswick M, Favara BE: Molecular studies of clonality indicate that Langerhans cell histiocytosis (LCH) is a clonal histiocytic neoplasm. Lab Invest 68:128A, 1993.
2. Broadbent V, Egeler RM, Nesbit ME: Langerhans cell histiocytosis—clinical and epidemiological aspects. Br J Cancer Suppl XXIII:S11–S16, 1994.
3. Writing Group of the Histiocyte Society. Histiocytosis syndromes in childhood. Lancet i:208–209, 1987.
4. Chu T, Jaffe R: The normal Langerhans cell and the LCH cell. Br. J. Cancer Suppl XXIII:S4–S9, 1994.
5. Emile J-F, Wechsler J, Brousse N, Boulland ML, Cologon R, Fraitag S, Voisin M-C, Gaulard P, Boumsell L, Zafrani E-S: Langerhans cell histiocytosis: Definitive diagnosis with the use of monoclonal antibody O10 in routinely paraffin-embedded samples. Am J Surg Path 19:616–641, 1995.
6. Dennis JW, Rosahn PD: The primary reticuloendothelial granulomas, with a report of an atypical case of Letterer-Siwe's disease. Am J Path 27:627–653, 1951.
7. Goldner MG, Volk BW: Fulminant normochoesterolaemic xanthomatosis. Arch Intern Med 95:689–698, 1955.
8. Perrot H, Garnier C, Claudy A, Thivolet J: Histiocytosis X chez un adult age. Bull Soc Fr Derm Syph 78:194–195, 1970.
9. Leques B, Verdaguer S, Tendil H, Limouzin F, Soustre L, Chenu V: Histiocytosis X cutanee et pulmonaire de l'adulte. Bull Soc Fr Derm Syph 78:57–59, 1971.
10. Shahani RT, Milford Ward A: Letterer-Siwe disease in a young adult. Brit J Derm 89:313–316, 1973.
11. Civatte J, Tsoitis G, Antsos N, Belaich S, Degos R: Maladie de Letterer-Siwe de l'adulte avec lesions ungueales. Bull Soc Fr Derm Syph 81:130–133, 1974.
12. Moulin G, Vaignat P, Bouchet P, Bonjean J, Jeune R, Bouvier R: Maladie de Letterer-Siwe chez un vieillard. Bull Soc Fr Derm Syph 82:353–354, 1975.
13. Feuerman EJ, Sandbank M: Histiocytosis X with skin lesions as the sole clinical expression. Acta Dermato-Venereol 56:269–277, 1976.
14. Kaufman A, Bukberg PR, Werlin S, Young IS: Multifocal eosinophilic granuloma (Hand-Schuller-Christian disease). Am J Med 60:541–548, 1976.
15. Benish B, Peison B, Carter H: Histiocytosis X of the skin in an elderly man. Am J Clin Path 67:36–40, 1977.
16. Amirdjazil Z, Esca S-A, Konrad K: Histiocytosis X in an adult with skin and uncommon central nervous system involvement. Dermatologica 155:283–291, 1977.
17. Chevrant-Breton J, Jambon N, Danrigal A, Kernel J, Labarthe B, Ferrand B: La maladie de Letterer-Siwe de l'adulte. Ann Dermato-Venereol 105:309–311, 1978.
18. Vollum DI: Letterer-Siwe disease in the adult. Clin Exp Dermatol 4:395–406, 1979.
19. Crowe MJ, O'Loughlin S, Noel J: Histiocytosis X with pulmonary and cutaneous manifestations (Letterer-Siwe disease) in an elderly woman. Ir J Med Sci 150:278–281, 1981.
20. Caputo R, Berti E, Mowti M, Gasparini G, Bertani E: Letterer-Siwe disease in an octogenarian. J Am Acad Dermatol 10:226–233, 1984.
21. Wright AL, Tucker WFG, Slater DN, Harrington CI: Letterer-Siwe disease in the ninth decade. J Amer Acad Dermatol 12:369–371, 1985.
22. Pareek SS, Hawass N-el-D: An unusual presentation of histiocytosis X. Internat J Dermatol 24:126–128, 1985.
23. Kuttner BJ, Friedman KJ, Burton CS, Olsen EA: Letterer-Siwe disease in an adult. Cutis 39:142–146, 1987.
24. Gaines P, Chan JCN, Cockram CS: Histiocytosis X involving the thyroid and hypothalamus. Postgrad Med J 67:680–682, 1991.
25. Lictenwald DJ, Jakubovic HR, Rosenthal D: Primary cutaneous Langerhans cell histiocytosis in an adult. Arch Dermatol 127:1545–1548, 1991.
26. Hasegawa K, Mitomi J, Kowa H, Motoori T, Yagisita S: A clinicopathological study of adult histiocytosis X involving the brain. J Neurol-Neurosurg Psych 56:1008–1012, 1993.
27. Yamashita H, Nagayama N, Kawashima M, Hidano A, Yamada O, Mizoguchi H: Langerhans cell histiocytosis in an adult patient with multiple myeloma. Clin Exp Dermatol 17:275–278, 1992.
28. Athanasou NA, Barbatis C: Erdheim-Chester disease with epipyseal and systemic disease. J Clin Path 46:481–482, 1993.
29. Case Records of the Massachusetts General Hospital. New Eng J Med 329:1108–1115, 1993.
30. Malpas JS: Langerhans cell histiocytosis in the adult—a presentation to the Nikolas Symposium (in press).
31. Avery ME, McAfee JG, Guild HG: Course and prognosis of reticulo-endotheliosis (eosinophilic granuloma, Schuller-Christian disease and Letterer-Siwe disease). Amer J Med 22:636–652, 1957.
32. Obermann HA: Idiopathic histiocytosis—a clinico-pathological

study of 40 cases and a review of the literature on eosinophilic granuloma of bone, Hand-Schuller-Christian disease and Letterer-Siwe disease. Pediatrics 28:307–327, 1961.
33. Enriquez P, Dahlin DC, Hayles PE, Henderson ED: Histiocytosis X, a clinical study. Proc Mayo Clinic 42:88–99, 1967.
34. Friedman PJ, Liebow AA, Sokoloff J: Eosinophilic granuloma of the lung. Medicine 60:385–396, 1981.
35. Webster SM, Unni KK, Beabout JW, Dahlin DC: Langerhans' cell granulomatosis (histiocytosis X) of bone in adults. Amer J Surg Path 6:413–425, 1982.
36. Broadbent B, Pritchard J: Etoposide VP-16 in the treatment of multi-system Langerhans cell histiocytosis (Histiocytosis X). Med Ped Onc 17:97–100, 1989.
37. Shin MS, Buchalter SE, Kang-Jey H: Langerhans cell histiocytosis associated with Hodgkin's disease—a case report. J Nat Med Ass 86:55–69, 1994.
38. Egeler RM, Neglia JP, Pucetti DM, Brennan CA, Nesbitt ME: Association of Langerhans cell histiocytosis with malignant neoplasms. Cancer 71:865–873, 1993.
39. Colby TV, Hoppe RT, Warnke RA: Hodgkin's disease: A clinicopathological study of 659 cases. Cancer 49:1848–1859, 1981.
40. Ben-Ezra JM, Koo CH: Langerhans cell histiocytosis and malignancies of the M-PIRE system. Hematopathology 99:464–471, 1992.